Clinical Findings and Prognostic Factors for Dogs Undergoing Cholecystectomy for Gall Bladder Mucocele

Sarah Malek[1], DVM, Elizabeth Sinclair[2], DVM, Giselle Hosgood[3], BVSc PhD FACVSc Diplomate ACVS, Noel M. M. Moens[2], DMV MSc Diplomate ACVS & ECVS, Trina Baily[1], DVM MS Diplomate ACVS, and Sarah E. Boston[1], DVM DVSc Diplomate ACVS

[1]Department of Companion Animals, Atlantic Veterinary College, University of Prince Edward Island, Canada, [2]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Canada, and [3]School of Veterinary and Biomedical Sciences, Murdoch University, Western Australia, Australia

Corresponding Author
Sarah Malek, DVM, Department of Companion Animals, Atlantic Veterinary College, University of Prince Edward Island, 550 University Avenue, Charlottetown, PE C1A 4P3 Canada
E-mail: smalek@upei.ca

Received March 2010
Accepted November 2011

DOI:10.1111/j.1532-950X.2012.01072.x

Objective: To report clinical findings and explore prognostic factors for dogs that had cholecystectomy for gall bladder mucocele.
Study Design: Retrospective case series.
Animals: Dogs (n = 43) with gall bladder mucoceles.
Results: Diagnosis of gall bladder mucoceles was confirmed by histopathology and 74% were diagnosed based on preoperative abdominal ultrasonography. Intraoperative evidence of gall bladder rupture was noted in 10 dogs (23%), and 16 (37%) had evidence of previous leakage in the abdominal cavity. One dog had positive bacterial growth from the gall bladder content. The most common histopathologic findings in liver biopsies obtained at surgery were cholangiohepatitis, biliary hyperplasia, or cholestasis. Univariate analysis showed evidence of postoperative hypotension ($P = .05$) to be significantly negatively associated with survival. Significant difference in mean postoperative serum lactate ($P = .034$) and postoperative packed cell volume ($P = .063$) between dogs that survived and died was also noted.
Conclusions: Elevations in postoperative serum lactate concentrations and immediate postoperative hypotension in dogs undergoing cholecystectomy for gall bladder mucoceles are associated with poor clinical outcome.

Although a recognized disease process for several decades, the incidence of gall bladder mucoceles (GM) in dogs appears to be increasing.[1,2] Whether this apparent increase is because of early-detection by improved abdominal ultrasonography, or an absolute increase in disease incidence, is unknown.

Defined as a mucus-filled distension of the gall bladder and associated with secretory dysfunction, GM can be life threatening.[2,3] Accumulation of viscous mucus within the gall bladder lumen can cause obstruction of the common bile duct (CBD), resulting in partial or complete obstruction.[2] Histologic diagnosis of GM is based on identification of cystic mucinous hyperplasia.[4] Progressive distension of the gall bladder may eventually cause pressure necrosis of the gall bladder or the bile duct, leading to rupture and subsequent bile peritonitis.[3,5] Obstruction secondary to the accumulated mucus can occur anywhere from the neck of the gall bladder to the extrahepatic biliary tree. The latter is a rarely reported consequence of biliary GM.[5] Although successful medical management of 2 non-severe cases of GM was recently reported,[6] cholecystectomy is generally indicated for GM causing biliary tract outflow obstruction. Cholecystectomy often involves flushing of the CBD before cystic duct ligation to ensure patency.[2,7,8] Techniques include flushing of the CBD either normograde catheterization by cholecystotomy before performing the cholecystectomy, or retrograde via the major duodenal papilla after duodenotomy.[7,9]

Although the reported perioperative mortality ranges from 21.7% to 40%,[1,2,8] the prognosis for a dog with GM undergoing cholecystectomy is generally favorable if the dog survives the immediate postoperative period.[1,2,10–12] Long-term outcome for dogs surviving surgery and the immediate postoperative period is good with 1 study reporting both 1- and 2-year survival rates of 22 of 34 (66%).[10] Our objectives were to report the clinical and intraoperative findings in dogs with GM undergoing cholecystectomy and to determine prognostic factors.

MATERIALS AND METHODS

Inclusion Criteria

A case search was performed at the Ontario Veterinary College (OVC) and Atlantic Veterinary College (AVC) for the terms cholecystectomy and/or GM over a 4-year time span (January 2004–August 2008). Inclusion criteria for this

Veterinary Surgery 42 (2013) 418–426

retrospective study included dogs with GM that had cholecystectomy and histologic confirmation of GM. Exclusion criteria included dogs that did not undergo cholecystectomy, dogs that underwent biliary diversion, and dogs that did not have a histologic diagnosis of GM. An ultrasonographic diagnosis was not an inclusion criterion for this study; however, ultrasonographic findings were recorded when available. The ultrasonographic diagnosis of GM was based on ultrasonographic evidence of a distended gall bladder with an immobile, nongravity dependent, stellate, or finely striated bile pattern.[1]

Data retrieved from medical records that included: age, weight, temperature, pulse and respiratory rate at time of presentation, gender, breed, acute clinical history, and concurrent medical problems. Ultrasonographic findings performed by the referring veterinarian and/or by the board-certified radiologist at the referral center were recorded. Intraoperative findings that included integrity of the gall bladder wall, presence or absence of gross appearance of gall bladder wall necrosis, presence or absence of bile leakage, presence or absence of CBD enlargement, presence or absence of choleliths in the CBD, whether or not the CBD was flushed and the method, surgical and general anesthesia time, and use of perioperative antibiotics, and postoperative administration of hepatoprotectant medications were recorded. The histologic description of gall bladder and other biopsy samples (primarily liver), complete blood count, and serum biochemical profile including serum lactate measurement results from the immediate pre- and postoperative period, and preoperative prothrombin time (PT), and partial thromboplastin time (PTT) if performed, were retrieved. Postoperative blood work results were included if they were performed within the first 24–48 hours after surgery, and the first recorded value in the immediate postoperative period was recorded for analysis. Results of microbial culture of samples taken from the gall bladder or the abdomen, or urine at the time of surgery were reviewed. Postoperative complications and duration of postoperative hospitalization were noted. Postoperative hypotension was documented as systolic blood pressure (<100 mmHg), and/or mean blood pressure (<60 mmHg) measured in the first 12 hours after surgery. Each blood pressure measurement was the result of at least 2 consecutive measurements using either a noninvasive oscillometric (Cardell) or sphygmomanometric (Doppler) device.

Follow-Up

When the dog died or was euthanatized, and the cause of death was recorded when available. For dogs that were discharged from the hospital, long-term follow-up was conducted via telephone interviews of referring veterinarians or owners.

Statistical Analysis

All categorical variables were summarized as frequencies and all numeric variables were summarized by quartiles, and mean ± SD (standard deviation). For survival information, death or euthanasia because of the gall bladder disease was considered as a complete event. All dogs that were alive at follow-up or died or were euthanatized for reasons unrelated to the gall bladder disease were right censored.

To explore the association of possible explanatory variables and survival, univariate analysis using Fisher's exact test (cell counts ≤ 5) or χ^2 (cell counts >5) for categorical variables and Student's t-test for numeric variables was performed comparing dogs that survived or died. Significant variables at $P < .10$ against a 2-sided hypothesis were then considered for entry into a multivariate Cox proportional hazards model (CPHM). Significant numeric variables on univariate analysis were categorized to allow for entry and useful interpretation in the multivariate models. Variables were kept in the model based on a significant Wald statistic at $P < .05$ such that the 95% confidence interval (95%CI) of the hazard estimate excluded 1.0. A stepwise selection was performed with inclusion of each variable set at $P < .2$ and retention in the model considered at $P < .05$. The model was run with different combinations of the significant variable to determine the simplest model of best fit, based on the smallest log-likelihood statistic. The final model was selected and the 95%CI of the conditional hazard was reported for included variables.

A Kaplan–Meier product limit estimate of overall survival was calculated and the 95%CI of the median and mean estimated survival times are reported. Software (SAS v9.1; SAS Institute, Cary NC) was used for the analysis.

RESULTS

Signalment

Forty-three dogs were included; 33 dogs from OVC and 10 from AVC. Breeds included Cocker Spaniel (10), Shetland Sheepdog (5), Miniature Schnauzer (4), Bichon Frise (5), mixed breed (3), Cock-a-Poo (2), Border Terrier (2), soft-coated Wheaten Terrier (2), Jack Russell Terrier and 1 each of Beagle, Yorkshire Terrier, Bernese mountain dog, Australian shepherd, Havanese, Labrador Retriever, Pekingese, Pomeranian, Toy Poodle. Mean (SD) age at the time of diagnosis was 9.64 (3.03) years. Mean (SD) body weight was 12.23 (8.7) kg. There were 24 spayed females (55.8%), 17 castrated males (39.5%), 1 intact male (2.3%), and 1 intact female (2.3%).

Clinical Findings

The most frequent clinical signs included vomiting (39 dogs; 90.7%), anorexia (31; 72.1%), and lethargy (35; 81.4%). Vital signs recorded on admission were mean (SD) heart rate of 120.07 beats/min (30.5); temperature, 38.7°C (0.83); and respiratory rate, 35 breaths/min (15.62).

Forty-two dogs had abdominal ultrasonography. One dog was referred for surgery after laparoscopic evidence of a

distended gall bladder and CBD was noted to be consistent with GM. Twenty-two dogs had abdominal ultrasonography by the referring veterinarian and a GM was diagnosed in 17 (77.3%). There were 35 dogs that had ultrasonographic examination performed by a board of certified radiologist; 23 had a GM (67.6%), and 12 dogs had findings not believed to be consistent with diagnosis of a GM. Fifteen dogs had an abdominal ultrasonography performed by both the referring veterinarian and a board-certified radiologist after referral. In 6 dogs, there was agreement between the findings of the referring veterinarian and the board-certified radiologist. Overall 35 of 42 (83.3%) of dogs had an ultrasound diagnosis of GM performed by either the board-certified radiologist, the referring veterinarian or both. In the 7 dogs that did not have an ultrasonographic diagnosis of GM, the decision to proceed with surgery were based on high index of suspicion for GM based on clinical signs, blood work abnormalities, suspected gall bladder abnormalities noted on ultrasonography (ie suspected peritonitis because of perforation of the gall bladder), and lack of clinical improvement despite supportive care.

Concurrent medical problems were present in 19 dogs and included one or more of the following conditions: hyperadrenocorticism (n = 4, 1 diagnosed at the time of presentation and 3 previously diagnosed and medically managed), controlled diabetes mellitus (n = 5, 1 newly diagnosed with concurrent diabetic ketoacidosis at the time of presentation), hypothyroidism (2, previously diagnosed and medically managed), hypoadrenocorticism (1, previously diagnosed and medically managed), adrenocortical carcinoma (1), urinary incontinence (1) pancreatitis (3; 2 in the postoperative period and 1 with chronic disease), lymphangectasia (1), cystic calculi with concurrent urinary tract infection (3), mitral valve disease (1), and tracheal collapse (1).

Intraoperative Findings

Intraoperative findings included observation of a viable intact gall bladder in 33 (76.7%) dogs. Areas of necrosis of the gall bladder wall were noted in 8 (18.6%) dogs; 7 had either a perforation of the gall bladder wall or evidence of prior leakage of bile material into the abdomen at the time of surgery. There was a evidence of previous bile leakage into the peritoneal cavity at surgery in 16 (37.2%) dogs where free bile was noted in the abdominal cavity or around the gall bladder with or without omental adhesions to the site of leakage. These 16 dogs all lived beyond 2 months after surgery. In dogs with free bile in the abdomen, the gall bladder appeared to be intact at the time of surgery in 6 dogs, and in the remaining 10 dogs a perforation was noted in the gall bladder. Intraoperative complications were leakage of bile during manipulation of the gall bladder in 3 (7%) dogs, 2 of which were because of rupture of the gall bladder while performing the cholecystectomy. The third dog already had a perforation of the gall bladder and a tear in the cystic duct that resulted in bile leakage intraoperatively. These complications were addressed by thorough lavage and aspiration of the abdominal cavity and placement of closed suction abdominal drains. These 3 dogs had no microbial growth from the gall bladder cultures obtained directly from the gall bladder content intraoperatively. One of these dogs had a positive bacterial culture of urine because of a preexisting urinary tract infection associated with uroliths that were removed via cystotomy at the time of surgery. These 3 dogs did not have any postoperative complications and had survival times more than 5 months. Other intraoperative findings were as followed: dilated CBD 10 of 37 (23.3%), dilated cystic duct 9(20.9%), tortuous cystic duct 1 (2.3%), choleliths 1 (2.3%) and liver nodules 3 (7%).

Patency of CBD was confirmed by normograde catheterization in 4 (9.3%) dogs and retrograde catheterization via duodenotomy in 16 (37.2%) dogs. The CBD was not catheterized in 23 (53.5%) dogs.

Mean (SD) anesthesia and surgical times were 153.4 minutes (48.7) and 101.5 minutes (42.0), respectively. Duration was prolonged in some cases when additional procedures were performed including jejunostomy tube placement, total or partial splenectomy, liver lobe resection, unilateral adrenalectomy, ovariohysterectomy, cystotomy for cystic calculi removal, and prophylactic gastropexy. No association was noted between the surgery and/or anesthesia time and survival.

Intraoperative antibiotics that were used intravenously included one of the following: ampicillin (22 mg/kg), cefazolin (22 mg/kg), cefoxitin (30 mg/kg), and enrofloxacin (10 mg/kg). Six (14%) dogs were not administered intraoperative antibiotics. Two dogs required re-exploration of the abdomen because of deterioration of clinical signs. One explored 2 days after initial surgery had leakage from a hepatic duct that was ligated without further complications and was alive at the time of writing (9 months postoperatively). The second dog was explored 6 days after initial surgery and an obstructed CBD identified. Retrograde catheterization of the CBD had been successful during the initial surgery. Retrograde catheterization was repeated during the second surgery and the CBD was stented using a 5-Fr feeding tube. The dog was discharged from the hospital 1 week later. One month after the second surgery, the owners elected to euthanatize the dog without any further work up because of a recurrence of the clinical signs, including vomiting, diarrhea, anorexia, and lethargy.

Postoperative Care

All dogs were treated postoperatively with intravenous fluids, intravenous pain medications varying from constant rate infusions or intermittent doses of opioids, and antiemetics as needed. Postoperative antibiotics were administered in 41 dogs and the remaining 2 dogs that did not receive antibiotics did not experience any complications in the postoperative period. Injectable antibiotics used in the postoperative period were the same as those used intraoperatively. Oral antibiotics administered postoperatively included: amoxicillin, amoxicillin/clavulanic acid,

cefaclor, cephalexin, and enrofloxacin. The class and type of oral antibiotic was the same as the parenteral one used. Short- or long-term cytoprotective agents were prescribed in 23 (53.5%) of the dogs and included ursodiol (ursodeoxycholic acid; 10–15 mg/kg/day orally) and/or s-adenosylmethionine (SAMe) (zentonil or denosyl; 20 mg/kg/day orally).

Microbiology and Histologic Findings

Bacterial culture and susceptibility testing was performed on the gall bladder contents of 37 dogs. Culture results were negative in 36 dogs (97.3%) and 1 dog had a 2+ growth of *Streptococcus alpha hemolytica*. This dog had received both intraoperative (ampicillin) and postoperative (cephalexin) antibiotics.

Urine culture and susceptibility testing was performed in 5 dogs yielded *Proteus mirabilis* (1 dog), and *Staphylococcus aureus* (1). The first dog had a history of urinary incontinence and was suspected to have a concurrent urinary tract infection at presentation. The second dog had concurrent uroliths that were removed via cystotomy at the time of cholecystectomy.

Microscopic examination of the gall bladder revealed cystic mucinous hyperplasia consistent with a GM in all dogs. Concurrent histologic findings in the gall bladder included: transmural necrosis (11), infarction (8), serosal fibrosis (4), lymphocytic plasmacytic cholecystitis (2), suppurative cholecystitis (2).

In 10 dogs where a perforation was noted at surgery, 80% had lesions consistent with necrosis of the gall bladder wall based on histopathology. Of these, 6 gall bladders had histopathologic evidence of mild-to-moderate transmural necrosis and 2 had evidence of infarction. Culture results of the gall bladder at surgery were available in 6 of 8 dogs that had histologic evidence of necrosis in the gall bladder wall. The only positive culture result from the gall bladder content was in 1 of these dogs with evidence of necrosis.

Results of liver biopsies were available for 37 (86.1%) dogs. The most frequent diagnoses were as followed: cholangiohepatitis (29.7%), biliary hyperplasia (29.7%), and cholestasis (29.7%), followed by the other histologic findings that are listed in Table 1.

Table 1 Histopathologic Findings of Liver Biopsies Obtained at the Time of Cholecystectomy in Dogs With Concurrent Gall Bladder Mucocele (n = 37)

Histopathologic finding	Number of dog (n)
Cholangiohepatitis	29.7% (n = 11)
Biliary hyperplasia	29.7% (11)
Cholestasis	29.7% (11)
Hepatic lipidosis	2.7% (1)
Portal fibrosis	21.6% (8)
Nodular hyperplasia	5.6% (2)
Vacuolated hepatopathy	2.7% (1)
Necrosis	8.1% (3)
Hepatic glycogenesis	8.1% (3)
Normal hepatic tissue	5.6% (2)
Portal hepatitis	10.8% (4)
Steroid induced hepatopathy	5.6% (2)
Multiple benign hepatic adenomas	2.7% (1)
Extramedullary hematopoiesis	1.9% (1)

Laboratory Findings

Preoperative hematologic and serum chemistry showed that mean total bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), and gamma-glutamyl transferase (GGT) concentrations were elevated above normal in all dogs regardless of survival (Table 2). For dogs in which amylase concentrations were measured preoperatively, elevated concentrations above the normal reference interval was present in 4 of 6 dogs that did not survive compared to 3 of 22 that survived; however, this difference was not statistically significant. The 2 postoperative blood work variables that had statistically significant variations between dogs that survived or died were the mean lactate concentration and packed cell volume (PCV). Lactate concentrations were measured preoperatively in 23 dogs (Table 2), and postoperatively in 24 dogs (Table 3).

Prognostic Factors

Postoperative blood pressure measurements were available in 34 dogs. Two dogs had postoperative hypotension (systolic blood pressure; <100 mmHg and/or mean blood pressure; <60 mmHg measured in the first 12 hours after surgery). The first dog did not respond to supportive care and was euthanatized 8 hours after surgery, and the second dog stabilized initially but relapsed with hypotension and was euthanatized because of development of pulmonary thromboembolism and multiple organ failure. Exploratory univariate analysis showed postoperative hypotension ($P = .05$) was significantly negatively associated with survival (Table 4). In addition, there was a significant difference in the mean postoperative serum lactate ($P = .034$) and postoperative PCV ($P = .063$) between dogs that survived and died (Table 3).

Variables that were entered into the CPHM were postoperative hypotension, postoperative lactate concentrations (increments of 1.0), and postoperative PCV (increments of 5%). Significant variables determined by the CPHM included postoperative hypotension ($P = .003$, hazard ratio: 20.4, 95% CI of hazard: 2.7–154.4) and postoperative serum lactate concentration (increments of 1.0) ($P = 0.014$, hazard ratio: 1.3, 95% CI of hazard: 1.1–1.6). Thus, if postoperative hypotension was present the risk of death was increased 20 times. The risk of death is also increased 0.3 times for each increment in lactate concentration in the postoperative period.

Follow-up

The overall estimated mean (SE) survival time was 7.43 (0.52) months. Median survival was not estimable overall

Table 2 Recorded Preoperative Blood Work the Group that Survived and Died after Surgery

	Survivors			Nonsurvivors			
Variable	Mean (range)	SD	N	Mean (range)	SD	N	Reference interval
Neutrophils	20.58 (5.75–86.6)	15.08	28	14.31 (4.96–31.48)	8.87	8	2.9–10.6 × 10^9/L
Bands	1.72 (0–21.24)	4.93	18	0.88 (0–3.29)	1.26	6	0.0–0.3 × 10^9/L
Na	147.1 (137–158)	4.98	31	144.5 (137–156)	5.63	8	140–154 mmol/L
K	4 (3.2–5.5)	0.6	30	4.08 (3.4–5.1)	0.66	8	3.8–5.4 mmol/L
Chloride	109.03 (96–125)	6.67	30	108 (100–123)	7.44	7	104–119 mmol/L
Albumin	30.53 (17–43)	5.92	33	30.38 (24–41)	5.24	8	29–43 g/L
Urea	7.14 (1.6–24)	5.88	33	6.08 (2.4–13.4)	3.57	9	3.5–9.0 mmol/L
Total bilirubin	63.71(1–208)	63.33	33	35.16 (2–152.3)	52.38	8	0–4 umol/L
ALP	2668.87 (158–8320)	2034.27	31	2365.29 (251–5014)	1465.25	7	22–143 U/L
ALT	913.57(21–3108)	786.12	23	393.67 (15–1535)	567.01	6	19–107 U/L
GGT	68.65 (0–454)	93.58	26	80.13 (0–424)	144.62	8	0–7 U/L
Amylase	936.05 (353–6314)	1217.53	22	1111.17 (532–2086)	577.02	6	299–947 U/L
Lipase	764.29 (79–5488)	1189.62	21	346.17 (166–475)	140.86	6	60–848 U/L
PT	10.52 (6.1–14.8)	3	17	9.87 (9.3–10.4)	0.55	3	9–15 seconds
PTT	20.74 (11–31.6)	6.39	17	19.97 (17.8–21.8)	2.02	3	15–23.5 seconds
Lactate	1.6 (0.7–3.6)	0.96	19	2.7 (1.5–3.6)	0.99	4	<2.0 mmol/L

Table 3 Mean (SD) Variables Significantly Different Between Dogs that Survived and Died based on Univariate Analysis ($P < .10$)

	Survived		Died/ euthanized		*P* value
Postoperative lactate concentration	1.2 (0.42)	n = 18	3.3 (5.0)	n = 6	.034
Postoperative PCV	37.2 (7.1)	n = 21	31.50 (8.1)	n = 7	.063

Table 4 Significant Categorical Variables Associated with Survival Based on Univariate Analysis at $P < .10$

Variable	Response levels	Survived	Died/ euthanatized	*P* value
Postoperative hypotension	Yes/no	Yes (n = 0) No (n = 24)	Yes (n = 2) No (n = 8)	.05

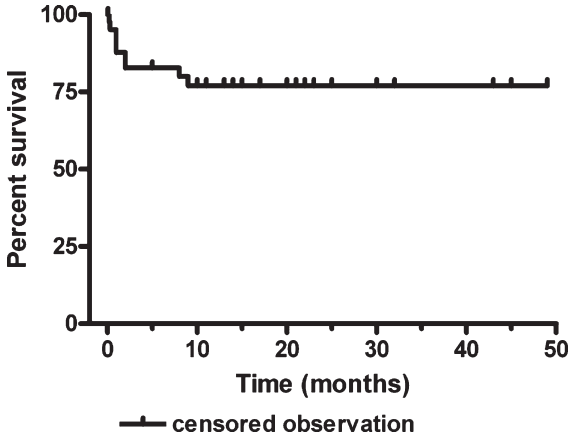

Figure 1 Estimated Kaplan–Meier survival functions for 43 dogs with gall bladder mucocele undergoing cholecystectomy. Ticks indicate censored observations.

because the probability of survival never approached 0.5. (Fig 1).

Three dogs died within 2 weeks of surgery; 2 died during hospitalization; and the third died 3 days after discharge. Of the 2 dogs that died in hospital, 1 was euthanatized 9 days after surgery because of development of pulmonary thromboembolism, multiple organ failure, and concurrent postoperative hypotension. This dog had had a well-differentiated adrenocortical carcinoma that had been removed without any complications at the time of cholecystectomy and had been suspected of having hyperadrenocorticism before surgery. The second dog had postoperative hypotension and anemia that was not responsive to treatment and euthanatized 8 hours after surgery. This dog had a history of chronic pancreatitis. The third dog had recurrence of vomiting and lethargy, and was euthanatized as the owners decided not to pursue further work up or treatment. Seven dogs lived more than 14 days after surgery but less than 2 months. Four of these dogs died or were euthanatized because of presumptive liver disease based on clinical deterioration at the referring veterinarian without further work up. Thirty-one dogs lived more than 2 months after cholecystectomy with an average survival time of 19 months; 21 were alive at the time of data collection and the mean survival time was 20.6 months. Ten dogs lived more than 2 months after surgery but were dead at the time of data collection; mean survival time was 19.3 months. Three dogs were euthanatized because of clinical signs attributable to liver disease, and other reported causes included suspected insulinoma, hyperadrenocorticism and hypothyroidism, neurological signs (suspected cervical spinal lesion), diabetes mellitus, mitral insufficiency, and hypocalcemia of unknown origin. One dog was lost to follow-up after 5 months and 1 immediately after discharge from the hospital.

Veterinary Surgery 42 (2013) 418–426

DISCUSSION

The signalment of dogs in this case series supports the breed distribution observed in previous reports on GM with a high number of Cocker Spaniels, Shetland Sheepdogs, and Miniature Schnauzers.[2] Clinical signs on presentation were often nonspecific with the most dogs having a combination of vomiting, lethargy, and anorexia. Icterus and abdominal pain have also been noted as common physical examination findings in other studies;[1,8] however, because of the retrospective nature of our study we did not obtain consistent information regarding presence or absence of these findings to include them in our data analysis.

There was a statistically significant difference in mean postoperative serum lactate concentrations ($P = .034$) and mean postoperative PCV ($P = .063$) of dogs that survived and died. Of these 2 variables, elevated postoperative lactate concentrations proved to be significant risk factors for death. The presence of lower mean postoperative PCV in dogs that died after surgery may have been a reflection of their general clinical status and concurrent medical problems. Previous studies have shown PTT times, serum concentrations of albumin, globulin, and bilirubin, percentage of band neutrophils, and total lymphocyte counts to also be risk factors for death[10,12,13] In the same studies, reported preoperative risk factors for death in dogs undergoing biliary surgery include age, preanesthetic heart rate, blood urea nitrogen, serum creatinine, GGT, phosphorus, and bilirubin values.[10,12]

The risk of death in our dogs increased 0.3 times (30%) for each increment in lactate concentration elevation in the postoperative period. Serum lactate concentrations have been previously investigated in dogs as a significant negative prognostic indicator in disease processes such as gastric dilatation and volvulus, and babesiosis.[14,15] The pathophysiology of elevated lactate concentration in dogs because of hepatic ischemia leading to impaired lactate removal has been demonstrated in previous studies.[16,17] Therefore, postoperative lactate concentration in dogs undergoing cholecystectomy for GMs may be used as an auxiliary monitoring and prognostic indicator.

The 2 dogs with postoperative hypotension were 20 times more likely to die than those without evidence of postoperative hypotension. The proposed underlying causes of postoperative hypotension include prolonged anesthesia, inadequate fluid administration, systemic inflammatory response syndrome (SIRS), and/or sepsis.[12] The postoperatively hypotensive dogs in our study were managed using crystalloid fluid therapy with or without colloid products, blood products such as fresh frozen plasma, packed red blood cells, and whole blood transfusions, as well as inotropes (eg dopamine), and vasopressors (eg norepinephrine) infusions as adjuvant support to control hypotension as needed. Both dogs that experienced clinical postoperative hypotension were euthanatized in the hospital because of poor response to treatment. It is more likely that the postoperative hypotension in these cases is a reflection of the overall status of the animal, since both dogs had other concurrent medical problems that would have attributed to the poor recovery and final outcome. Although association between hypotension and death of the animal must be interpreted with caution as both dogs were euthanatized because of lack of response to treatment. Because of the limitations associated with a retrospective study, we were also unable to evaluate postoperative blood pressure in comparison to pre- and intraoperative blood pressures while taking into account other factors that may affect these measurements such as anesthetic drug protocol. Our finding, however, supports a previous report that found postoperative hypotension to be a significant risk factor for mortality in cases undergoing extrahepatic biliary surgeries.[12] It therefore, warrants careful perioperative monitoring of cases undergoing cholecystectomy, to allow early detection and aggressive management.

All 35 dogs (83.3%) that had ultrasound performed with diagnosis of GM based on either the primary veterinarian or the board-certified radiologist at the referral center were confirmed by histopathologic examination of the excised gall bladder. The other 7 dogs did not have typical ultrasound features associated with GM, but were explored surgically because of high index of suspicion based on clinical signs. In a study of 14 dogs, the ultrasonographic evidence of finely striated and stellate bile patterns was consistently associated with macroscopic diagnosis of mucoceles.[1] In that study, the 10 dogs that had histologic examination of the excised gall bladder were confirmed histologically as GMs. Previous studies have shown the ultrasonographic features of echogenic, immobile material in the gall bladder with a striated, stellate, or mixed pattern to be diagnostic for GMs.[1,2] These findings highlight the value of ultrasound examination of dogs with suspected gall bladder disease as highly sensitive diagnostic tool. In people, despite availability of advanced imaging modalities (e.g. MRI, CT), ultrasonography remains a highly used diagnostic tool as an inexpensive, quick, and noninvasive screening test with good to high sensitivity, specificity, and diagnostic accuracy in many types of biliary diseases.[18]

In 10 dogs, the gall bladder wall was grossly not intact at surgery and 80% had lesions consistent with necrosis of the gall bladder wall based on histopathology. Of these, 6 gall bladders had histopathological evidence of mild-to-moderate transmural necrosis and 2 had evidence of infarction. Severe, diffuse transmural necrosis of the gall bladder wall has been classified as gall bladder wall infarction with unique histologic appearance and shown to carry a guarded prognosis with 33% mortality rate in a study of 12 cholecystectomized dogs.[19] The current case series did not reveal any correlation between gall bladder wall necrosis and survival in the postoperative period. Other studies have also shown positive bacterial culture results to be as high as 70%, and up to 81.3% when evidence of gall bladder wall necrosis is histologically present.[13,20] Bacterial culture results of the gall bladder at the time of surgery in our study was available for 6 of 8 dogs with histologic evidence

of necrosis in the gall bladder wall, and was positive for bacterial growth in only 1 dog.

The only positive bacterial culture was obtained from the contents of a gall bladder that was intact at surgery and had no gross evidence of prior leakage. This dog had been administered intra- and postoperative antibiotics. The use of perioperative antibiotics in 95.4% of our dogs may have been a confounding factor in decreasing the number of positive cultures, as suggested by another study.[2] In one large multicenter study, the use of antimicrobial prophylaxis in laparoscopic and conventional cholecystectomy in people decreased perioperative morbidity rate and shortened duration of hospitalization.[21] Peri- and postoperative antibiotic administration is recommended in dogs undergoing gall bladder surgery, particularly when there is a suspicion of gall bladder rupture, because of evidence of enteric bacteria that are cultured from the gall bladder contents at the time of surgery.[2,22] Previous studies looking at bacterial culture results at the time of gall bladder removal because of GM have shown controversial results with positive cultures as high as 66.7% (6 of 9),[1] and 14.0% (1 of 7)[8] to as low as 9.1% (2 of 22)[2] in another study. However, in the first study, the extent of perioperative use of antibiotics was not elaborated upon and, therefore, comparison of these findings may be difficult. Higher rates of positive culture results have been reported when other surgically treated biliary diseases have been investigated with reports as high as 35–50%.[12,22]

Gall bladder rupture can result from physical distension of the gall bladder and subsequent ischemic necrosis of the gall bladder wall that can lead to leakage into the peritoneal cavity resulting in septic or aseptic bile peritonitis, depending on the gall bladder content. Mortality rates for dogs with septic bile-induced peritonitis and dogs with aseptic peritonitis have been reported to be 55–73% and 0–13%, respectively, based on different studies.[12,23] However, one study of 45 dogs with gall bladder disease that had a 40% rate of confirmed gall bladder rupture did not find any evidence supporting septic or aseptic bile leakage from gall bladder rupture at initial surgical intervention being a negative prognostic factor.[13] That study also found lower mortality rates attributable to preoperative bile leakage (5.5%)[13] compared to other studies that have reported 28–39% mortality rates after surgery for bile peritonitis.[2,8,13,20] Based on the majority of the studies, prevention of secondary bacterial infection, which substantially worsens the prognosis for dogs with bile-induced peritonitis, is an important rationale for early surgical intervention when gall bladder rupture is suspected.[2,23] In our study, evidence of gall bladder leakage was not associated with mortality.

Concurrent liver abnormalities such as cholangiohepatitis have been a common histologic finding on the liver samples obtained at cholecystectomy both in our dogs and in a previous study.[8] In our dogs, 94.4% of the liver samples had some abnormalities on histologic examination; 11 had evidence of cholangiohepatitis. Use of cytoprotective agents such as SAMe and ursodiol is controversial in cases with hepatobiliary disease. The effects of SAMe administration in hepatobiliary disease have been evaluated in animal models and human clinical trials.[24–27] Unfortunately, because of lack of published clinical trials, true therapeutic potentials of this drug in companion animals with hepatobiliary disease are largely unknown. However, based on the nature of hepatobiliary disease in dogs, it has been recommended as an adjunctive treatment of many hepatobiliary disorders including cholestatic diseases such as GM, cholecystitis, and cholelithiasis.[24–27] Ursodiol is also advocated in intra- and extrahepatic cholestasis in absence of complete bile duct obstruction.[28] Some of the known properties of ursodiol include: choleretic activity, antiapoptotic, and immunomodulatory properties.[28] Although used extensively in animal models of hepatotoxicity, little information is available on use of ursodiol in small animals.[6,29] There is some evidence both *in vitro* and *in vivo* that the actions of SAMe and ursodiol may be additive.[30,31] Cytoprotective agents were used in 53.5% of the dogs in our study. There was no apparent protective effect of this treatment with respect to survival; however, because of lack of randomization of the treatments, the relatively high overall survival rate and the retrospective nature of the study, it is possible that these medications may have a beneficial effect that was not determined by this study. Long-term follow-up of the duration of long-term treatment with these medications were also not determined. Ongoing hepatic disease may play a role in postoperative prognosis of cases undergoing cholecystectomy, therefore, long-term follow-up of these cases, through blood work and ultrasound rechecks, may allow more aggressive treatment of the liver pathologies that may be present concurrently with the GM.

Recent studies have reported data that have noted the prevalence of concurrent endocrinopathies in dogs that have GM.[22,32] Studies have reported a relatively high number of dogs with hypothyroidism (13%),[22] and hyperadrenocorticism (23% and 21%)[22,32] at the time of GM diagnosis. One retrospective case control study showed no statistically significant association between the GM and presence of diabetes mellitus, but significantly higher prevalence of hypothyroid and hyperadrenocorticism in cases with GM, compared to the matched control group.[32] In our cases series, 9.3% hyperadrenocorticism, 4.7% hypothyroidism, and 11.7% diabetes mellitus cases were documented at the time of presentation for GM. The true incidence of endocrinopathies in our case series cannot be determined because of its retrospective nature and lack of complete laboratory follow-up on every case. However, there are no studies that have shown the role of either of these endocrinopathies in the pathogenesis of GM. It is also possible that this prevalence of endocrinopathies would exist if we were to examine a breed, sex, and age-matched cohort of dogs in our hospital population.

No significant association was found between the methods of catheterizing the CBD during cholecystectomy and whether or not the CBD was catheterized. This result, while noted, has the potential for bias because the decision to catheterize the CBD and the method of catheterization was likely based on the opinion of the attending surgeon

as well as the intraoperative findings. A prospective randomized clinical trial would be necessary to determine the necessity of catheterization of the CBD in cases of GM and recommendations on the necessity or technique for flushing the CBD during surgery cannot be made based on our findings.

Limitations of our study included the retrospective nature of the study that resulted in the lack of randomization and controls in treatments and techniques. In addition, consistent long-term follow-up is difficult because of the nature of the study. In cases of death after discharge from the hospital, the underlying cause of death could not be determined definitively in most cases because of lack thorough clinical work up or necropsy.

The immediate postoperative mortality rate (within 2 weeks of surgery) after cholecystectomy was 7% (3 of 43) that is reduced compared to the previously reported 22–40%.[1,2,11,12] This decrease may be explained by our exclusion of cases undergoing biliary diversion surgeries. We also excluded any cases that lacked histologic confirmation of a GM. It has been shown in previous studies that dogs that survive the immediate postoperative period after cholecystectomy appear to have an excellent prognosis for survival[2] that is supported by our study.

Our findings indicate that evidence of postoperative elevations in serum lactate levels, and postoperative hypotension was significantly associated with mortality. Monitoring of these variables is recommended in these dogs, to allow early detection and intervention to help improve survival rates after cholecystectomy for GM in dogs.

REFERENCES

1. Besso JG, Wrigley RH, Gliatto JM, et al: Ultrasonographic appearance and clinical findings in 14 dogs with gallbladder mucocele. *Vet Radiol Ultrasound* 2000;41:261–271
2. Pike FS, Berg J, King NW, et al: Gallbladder mucocele in dogs: 30 cases (2000–2002). *J Am Vet Med Assoc* 2004;224:1615–1622
3. Harkema JR, Mason MJ, Kusewitt DF, et al: Cholecystotomy as treatment for obstructive-jaundice in a dog. *J Am Vet Med Assoc* 1982;181:815–816
4. Kovatch RM, Hildebra PK, Marcus LC: Cystic mucinous hypertrophy of mucosa of gall bladder in dog. *Pathol Vet* 1965;2:574–584
5. Newell SM, Selcer BA, Mahaffey MB, et al: Gallbladder mucocele causing biliary obstruction in two dogs: ultrasonographic, scintigraphic, and pathological findings. *J Am Anim Hosp Assoc* 1995;31:467–472
6. Walter R, Dunn ME, d'Anjou MA, et al: Nonsurgical resolution of gallbladder mucocele in two dogs. *J Am Vet Med Assoc* 2008;232:1688–1693
7. Martin R, Lanz O, Tobias K: Liver and biliary system, in Slatter D (ed): *Text book of small animal surgery* (ed 3). Philadelphia, PA, Saunders, 2003, pp 710–726
8. Worley DR, Hottinger HA, Lawrence HJ: Surgical management of gallbladder mucoceles in dogs: 22 cases (1999–2003). *J Am Vet Med Assoc* 2004;225:1418–1422
9. Fossum T, Hedlund C, Hulse D, et al: *Small animal surgery* (ed 3). St. Louis, MO, Mosby, 2007, pp 560–572
10. Amsellem PM, Seim HB, MacPhail CM, et al: Long-term survival and risk factors associated with biliary surgery in dogs: 34 cases (1994–2004). *J Am Vet Med Assoc* 2006;229:1451–1457
11. Cornejo L, Webster CRL: Canine gallbladder mucoceles. *Compend Contin Educ Pract Vet* 2005;27:912–928
12. Mehler SJ, Mayhew PD, Drobatz KJ, et al: Variables associated with outcome in dogs undergoing extrahepatic biliary surgery: 60 cases (1988–2002). *Vet Surg* 2004;33:644–649
13. Crews LJ, Feeney DA, Jessen CR, et al: Clinical, ultrasonographic, and laboratory findings associated with gallbladder disease and rupture in dogs: 45 cases (1997–2007). *J Am Vet Med Assoc* 2009;234:359–366
14. de Papp E, Drobatz KJ, Hughes D: Plasma lactate concentration as a predictor of gastric necrosis and survival among dogs with gastric dilatation-volvulus: 102 cases (1995–1998). *J Am Vet Med Assoc* 1999;215:49–52
15. Nel M, Lobetti RG, Keller N, et al: Prognostic value of blood lactate, blood glucose, and hematocrit in canine babesiosis. *J Vet Intern Med* 2004;18:471–476
16. Arieff AI, Park R, Leach WJ, et al: Pathophysiology of experimental lactic acidosis in dogs. *Am J Physiol* 1980;239:135–142
17. Berry MN, Scheuer J: Splanchnic lactic acid metabolism in hyperventilation metabolic alkalosis and shock. *Metab Clin Exp* 1967;16:537–547
18. Gandolfi L, Torresan F, Solmi L, et al: The role of ultrasound in biliary and pancreatic diseases. *Eur J Ultrasound* 2003;16:141–159
19. Holt DE, Mehler S, Mayhew PD, et al: Canine gallbladder infarction: 12 cases (1993–2003). *Vet Pathol* 2004;41:416–418
20. Church EM, Matthiesen DT: The surgical-treatment of 23 dogs with necrotizing cholecystitis. *Vet Surg* 1987;16:85–85
21. Lippert H, Gastinger J: Antimicrobial prophylaxis in laparoscopic and conventional cholecystectomy. Conclusions of a large prospective multicenter quality assurance study in Germany. *Chemotherapy* 1998;44:355–363
22. Aguirre AL, Center SA, Randolph JF, et al: Gallbladder disease in Shetland Sheepdogs: 38 cases (1995–2005). *J Am Vet Med Assoc* 2007;231:79–88
23. Ludwig LL, McLoughlin MA, Graves TK, et al: Surgical treatment of bile peritonitis in 24 dogs and 2 cats: a retrospective study (1987–1994). *Vet Surg* 1997;26:90–98
24. Lieber CS: S-adenosyl-L-methionine: its role in the treatment of liver disorders. *Am J Clin Nutr* 2002;76:1183S–1187S
25. Manzillo G, Piccinino F, Surrenti C, et al: Multicentre, double-blind, placebo-controlled study of intravenous and oral S-adenosyl-L-methionine (SAMe) in cholestatic patients with liver disease. *Drug Invest* 1992;4(Suppl 4):90–100
26. Mato JM, Lu SC: Role of S-adenosyl-L-methionine in liver health and injury. *Hepatology* 2007;45:1306–1312

27. Webster CR, Boria P, Usechak P, et al: S-adenosylmethionine and cAMP confer differential cytoprotection against bile acid-induced apoptosis in canine renal tubular cells and primary rat hepatocytes. *Vet Ther* 2002;3:474–484
28. Webster CRL, Cooper J: Therapeutic use of cytoprotective agents in canine and feline hepatobiliary disease. *Vet Clin North Am Small Anim Pract* 2009;39:631–652
29. Meyer DJ, Thompson MB, Senior DF: Use of ursodeoxycholic acids in a dog with chronic hepatitis: effects on serum hepatic tests and endogenous bile acid composition. *J Vet Intern Med* 1997;11:195–197
30. Binder T, Salaj P, Zima T, et al: Randomized prospective comparative study of ursodeoxycholic acid and S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis of pregnancy. *J Perinatal Med* 2006;34:383–391
31. Milkiewicz P, Mills CO, Roma MG, et al: Tauroursodeoxycholate and S-adenosyl-L-methionine exert an additive ameliorating effect on taurolithocholate-induced cholestasis: a study in isolated rat hepatocyte couplets. *Hepatology* 1999;29:471–476
32. Mesich MLL, Mayhew PD, Paek M, et al: Gall bladder mucoceles and their association with endocrinopathies in dogs: a retrospective case-control study. *J Small Anim Pract* 2009;50:630–635